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**THE COUNCIL FOR TOBACCO RESEARCH-U.S.A., INC.**

110 EAST 58TH STREET  
NEW YORK, N.Y. 10022  
(212) 421-8885

Application for Research Grant  
(Use extra pages as needed)

Date:

1. Principal Investigator (give title and degrees):

Goro Mimura, M.D. Associate professor

2. Institution & address:

Institute of Constitutional Medicine, Kumamoto University.  
4-24-1, Kuhonji, Kumamoto City, Japan.

3. Department(s) where research will be done or collaboration provided:

Department of Geriatrics.

4. Short title of study:

The International Collaborative Twin Registry.

5. Proposed starting date: 1st, July, 1974.

6. Estimated time to complete: 30th, June, 1977.

7. Brief description of specific research aims:

The purpose of the research is the registry of twins in Kumamoto Prefecture according to the method of international twin registry. And by using the twins who were registered, this study aims at evaluation of the interactions between genetic, environmental factors including smoking and their associations with disease, especially ischemic heart disease.

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**8. Brief statement of working hypothesis:**

Hereditary factors as well as environmental factors bring on ischemic heart disease. Therefore, to determine the influence of hereditary and environmental factors (including smoking) on health condition and disease, the study of monozygotic twins is most useful and even necessary.

**9. Details of experimental design and procedures (append extra pages as necessary)**

Experimental procedure of twin study

1) The registry procedure of twins

Three methods are considered for compiling a twin registry in Kumamoto Prefecture, Japan. One is based on census registration, the second on a mailing of questionnaires to all householders in Kumamoto Prefecture, and the third is based on solicitation of twin volunteers through local health centers. Kumamoto Prefecture has about 1,700,000 inhabitants in 450,000 households. Of these about 980,000 persons are 25 years of age or older. The rate of twin births in Japan is approximately 0.6 %, and among all twin births about 68 % are monozygotic. In the Kumamoto population consisting of people 25 years or older, about 2900 twin pairs would be expected. Of these about 1,900 pairs would be monozygotic. A unique feature of a twin register in Japan would be the possibility of finding twins reared apart from the time of birth. In the past it was not uncommon that twins were separated at birth by one of them being placed in another family. The best method to find such twins would probably be the use of birth certificates and census registration records in addition to the information from local health centers. Birth records can be linked to population records through residence data. In the case of using birth records, it is impossible to detect the present address of twins. Therefore, in order to detect twins, the best way is to use the census registration system in Japan.

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But since World War II there are some disadvantages in this system, for detecting twin pairs. Namely, in the case where children get married the family register of children must be separated from the register of parents. If parents die, the family register of parents disappears from the present census registration. In the case where twin partners over the age of 25 got married and their family registers were separated from each other since 1948, the probability of the detection of twins over the age of 25 in the first stage of the examination will be very small.

Therefore, in the second stage of the examination I must go back to the past family register of their parents. As the pilot study I have investigated with the permission of the Ministry of Justice the past family registers of Kumamoto City which includes all family members. From the result of our pilot study, in order to find twin pairs from the investigation of family registers, at least two years and 4 person's work will be necessary. It will take about two minutes to check one family register. From our present study we found about one twin pair per one hundred past family registers for 460,000 people in Kumamoto City. Therefore, calculating from about 1,700,000 inhabitants of Kumamoto Prefecture, the number of past family registers will amount to 480,000.

The rate of twin pairs which will be obtained from the past family registers will be one per cent, but the past family registers range from 1868 to 1947. About half of the twin pairs which we detected from the past family registers in Kumamoto City have already died. Therefore, the rate of finding twins from the investigation of the past family registers will be about 0.5 or 0.6 per cent. This percentage will not be very different compared with that obtained from the birth rate. After we have detected the twin pairs over 25 years old from the past family registers, as the second stage of the study we must investigate the new family registers of twins and we will find the address of twin pairs.

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As there are about 480,000 past family registers in Kumamoto Prefecture, and as those are preserved in 10 cities, 30 towns and 58 village offices, the task of investigating all those family registers is not a small one. At the same time, we will gather information about twins from the health centers and other organizations.

After registry of twins, we will send the questionnaire to the twin partners.

2) The diagnosis of zygote in Japan

The degree of precisely diagnosing zygote is the fundamental problem in this study. The method of diagnosis which is used in my Institute is as follows. In order to diagnose the zygote, apart from anthropometrical measurement, the character of independent blood typing (ABO and MN blood type and Rh factor), finger-printing, phenyl-thio-carbamide test (PTC test), mid digital hair test (with or without) and earwax test (dry earwax or wet earwax) will be necessary. In the PTC test, after administering PTC drops on the tongue, two groups are divided according to the presence or absence of bitterness. Final diagnosis of Zygote is made from the combination of all above-mentioned factors. The diagnosis of monozygotic twins is made in the case where the blood typing is concordant and other characters also are concordant. In all other cases, the diagnosis is made as dizygotic twin. There are certain criteria of concordance in fingerprinting. In other countries, it has been reported that the diagnosis of zygote based on the information record and the twins' opinions was the best method. But in Japan the condition is a little different in adult twins, because in the past people believed all monozygotic twins to be same-sexed. Therefore, in Japan in the case of adult twins, it is unknown what degree of probability of zygosity diagnosis I can get by only the twins' opinions of Zygosity. As for this problem, because the number of twins I have examined is not suffi-

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cient, at this stage I would like to refrain from a conclusion, but it is presumed that the degree of precisely diagnosing Zygote will decrease in Japan compared with that in other countries. For the above mentioned reasons, in the diagnosis of Zygote it is necessary to perform the examination of blood typing and other examinations if at all possible, in addition to twins' opinions. About one hour will be necessary to diagnose the Zygote. Therefore, two years will be necessary for this work.

3) The necessity of taking electrocardiogram

In Japan the death rate due to heart disease has increased during the past twenty years and heart disease is now third among the causes of death. It is presumed that this tendency is due to the increase of old age population, Europeanization of the mode of living and other circumstantial factors. In 1950 the death rate from ischaemic heart disease was 9.9 per cent per 100,000 population, but in 1962 and 1967 it was 19.8 and 30.3, respectively, but compared with the death rate from ischaemic heart disease in the U.S.A. the rate in Japan is only one tenth. And most of the ischaemic heart disease is without pain so typical angina pectoris and myocardial infarction are relatively few compared with those in Europe and U.S.A. We may possibly miss a big number of ischaemic heart disease without pain when we use only this questionnaire in Japan. Therefore, I think electrocardiogram examination including exercise is necessary to cover all ischaemic heart disease cases. When the twin partner will come to our Institute, the electrocardiogram will be performed easily, but it will be difficult, for our research fellows to go to other cities, towns and villeges.

As can be understood from the above mentioned reasons, the social condition of twins in Japan is different in several points compared with that in other countries. Therefore, in order to cooperate with the international collaborative study of twins it is necessary and it would be appreciated if the special character of twins in Japan could be given due consideration.

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## 10. Space and facilities available (when elsewhere than item 2 indicates, state location):

The Institute of Constitutional Medicine is a five storey building (3240.0 m<sup>2</sup>). Half of the second floor belongs to our department alone. We have also the use of all the fifth floor which includes the laboratory. In the lab. there is the usual equipment e.g., autoanalyzer, spectrometer, fluorescentmeter, electromicroscope etc. As our department takes care of in and out patients in the adjoining University Hospital, we have the use of the lab. and equipment there.

to diagnose the twins. Therefore, it will be necessary

## 11. Additional facilities required:

In order to examine and blood type the twins all over Kumamoto Prefecture we will require the use of the facilities of the different hospitals affiliated with our Institute. There are four such hospitals in Kumamoto Prefecture. We will also use and require the cooperation of 16 Health Centers in the Prefecture.

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## 12. Biographical sketches of investigator(s) and other professional personnel (append):

## 13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

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The Institute of Constitutional Medicine is a day school.

which includes the Curriculum Vitae  
equivalent of several hours preparation and out  
electrocardiogram etc. at our disposal. Date: Jan. 26, 1974  
patients in the affiliated University Hospital and in the

1. Name : Goro Mimura

2. Date of Birth: **REDACTED**

3. Sex : Male

4. Address **P  
REDACTED**

5. Present Position and Institution:-

Associate Professor, Department of Geriatrics,  
Institutional Medicine, Kumamoto University,  
Japan.

6. Medical School Education:

In addition Kumamoto Medical College, 4 years.

7. Post Graduate Training after Internship:

such hospitals, Medical Staff, 3 years, Kumamoto University.

Assistant, 2 years, same Department.

Assistant Professor, 2 years, same Department.

Associate Professor, 12 years, same Department.

Goro Mimura

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KUMAMOTO, JAPAN

Curriculum Vitae

Date: Jan. 26, 1974

1. Name : Tomio Jinnouchi

2. Date of Birth: **REDACTED**

3. Sex : Male

4. Address : **REDACTED** **REDACTED**

5. Present Position and Institution:

Assistant Professor, Department of Geriatrics,  
Institutional Medicine, Kumamoto University,  
Japan.

6. Medical School Education:

Kumamoto Medical Collage, 4 years.

The postgraduate course, 4 years.

7. Post Graduate Training after Internship:

Assistant, 3 months, Kumamoto University.

Assistant Professor, 8 years, same Department.

Tomio Jinnouchi

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KUMAMOTO, JAPAN

Curriculum Vitae

Date: Jan. 26, 1974

1. Name : Shoji Fukumitsu
2. Date of birth: **REDACTED**
3. Sex : Male
4. Address : **REDACTED**  
**REDACTED**

5. Present Position and Institute:

Chief of Department of Cardiovascular  
Disease and Main staff of Diabetes Clinic.  
Yatsushiro Sogo General Hospital.  
(Affiliated hospital to School of Medicine  
and Research Institute of Constitutional  
Medicine, Kumamoto University )

6. Medical School Education:

Graduated A from Medical School of  
Kumamoto University after four years full  
educational curriculum.

7. Postgraduate training after internship:

1955--1959 Medical Staff

Clinical trainig and research study in  
cardiovascular disease and diabetes at  
Department of Geriatrics, Research Institute  
of Constitutional Medicine, Kumamoto University.

1959--1960 Assistant

Same as above

1960--1962 Clinival activities at Hiwatari  
Clinic in Kagoshima city.

Since December 25, 1962 at present position and  
the Hospital.

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*Shoji Fukumitsu*

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Curriculum Vitae

Date : Jan. 26, 1974

1. Name : Haraguchi Yoshikuni

2. Date of Birth:

3. Sex : Male

4. Address :

5. Present Position and Institution:

Chief, Department of Cardiology, National  
Kumamoto Hospital, Japan.

6. Medical School Education:

Kumamoto Medical Collage, 4 years.

The postgraduate course, 4 years.

7. Post Graduate Training after Internship

Assistant Professor, 1 years, Kumamoto University.

Chief, 2 years, Oita Prefectual Hospital.

Chief, 6 years, National Kumamoto Hospital.



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KUMAMOTO, JAPAN

Curriculum Vitae

Date: Jan, 26, 1974

1. Name : Keizo Kajiwara

2. Date of Birth: **REDACTED**

3. Sex : Male

3. Sex : Male

4. Address : **REDACTED** **REDACTED**

5. Present Position and Institution:

Medical Staff, Department of Geriatrics,

Institutional Medicine, Kumamoto University,

Japan.

6. Medical School Education:

Kumamoto Medical Collage, 4 years.

7. Post Graduate Training after Internship:

Medical Staff, 2 years, Kumamoto University.

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Keizo Kajiwara

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Publications:

- 1) Miyao, S. and Mimura, G.: On the morbidity in twins with special regard to malignant tumor and metabolic disease. Bull. of the Institute of Constitutional Medicine, Kumamoto Univ. 18:137 1967.
- 2) Mimura, G. Miyao, S., Koganemaru, K., Haraguchi, Y., Jinnouchi, T. and Hashiguchi, J.: Heredity of diabetes mellitus in Japan. Diabetes Mellitus in Japan. Excerpta Medica Intern. Series. No.221:83, 1970.
- 3) Mimura, G.: Epidemiology of diabetes in Asia, especially in Japan.: Diabetes, Excerpta Medica Intern. Series No.231:331, 1970.
- 4) Mimura, G. and Kodera, M.: Genetic study on essential hypertension. Japanese Circulation J. 37:61, 1973.
- 5) Mimura, G.: Study of twins with hypertension. Singapore Med.J. 14:278, 1973.

Kumamoto Medical College, Faculty of Medicine, Kumamoto University

Medical Staff, 2 years, Kumamoto University

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## 14. First year budget:

A. Salaries (give names or state "to be recruited")  
 > Professional (give % time of investigator(s)  
 even if no salary requested)

Dr. Goro Mimura	30	-
Dr. Tomio Jinnouchi	25	-
Dr. Shouji Fukumitsu	15	-
Dr. Yoshikuni Haraguchi	20	-
Dr. Keizo Kajiwara	20	-

## Technical:

Lab. Technician(1) (to be recruited)	100	3333
Typist(1) (to be recruited)	100	3333
Registration Staff(3) (to be recruited)	80	5000

Sub-Total for A 11666

## B. Consumable supplies (by major categories)

Paper and Printing Fee (Questionnaire etc)	3000	<i>31517.2</i>
Postage and Telephone	1500	<i>16</i>
Blood Typing Chemicals etc	1333	<i>17</i>

Sub-Total for B 5833

## C. Other expenses (itemize)

Reward for cooperation (twins)	13330
Travel Expenses	6665

Sub-Total for C 19995

Running Total of A + B + C 37494

## D. Permanent equipment (itemize)

Sub-Total for D	<u>0</u>
E	<u>5624.8</u>

Total request 43118.8 dollars

## E. Indirect costs (15% of A+B+C)

## 15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	11666	5833	53333	0	10624.8	81456.8
Year 3	6666	1660	53333	0	9248.85	70907.85

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## 16. Other sources of financial support

List financial support from all sources, including own institution, for this and related research projects.

## CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
The study of twins	Institute of Constitutional Medicine, Kumamoto University	5000	Jan. 1. 1974 to Dec. 31. 1974

## PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

## Principal investigator

Typed Name Goro Mimura *[Signature]*

Signature *Goro Mimura* Date 26th Jan.  
1974

Telephone 0963 63-1111 3762

Area Code Number Extension

## Responsible officer of institution

Typed Name Yoshitaka Harada

Mailing address for checks Department of Geriatrics, Title Director of Institute of Constitutional Medicine, Signature *Y. Harada* Date 26th Jan.

Institute of Constitutional Medicine, Kumamoto University, 4-24-1, Kuhonji, Kumamoto City, Japan.

Telephone 0963 63-1111 3711

Area Code Number Extension

Checks payable to

Goro Mimura, M.D., Associate professor

Institute of Constitutional Medicine, Kumamoto University, 4-24-1, Kuhonji, Kumamoto City, Japan.

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